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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/758,033	11/27/1996	GARY L. CLAYMAN	INGN:022	5378

7590 02/23/2005

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/758,033	CLAYMAN, GARY L.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16-20,26-32,36,37 and 146-150* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,16-20,26-32,36,37 and 146-150* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: fax copy of interview 12/1/04

DETAILED ACTION

This application filed November 27, 1996, claims benefit to provisional application 60/007,810, filed November 30, 1995.

The previous office action mailed June 3, 2004, **is vacated** and new office action on the merits is set forth below. As indicated in the interview summary of December 1, 2004, issued raised during a previous discussion with Applicants will be addressed.

Claims 1-14, 16-20, 26-32, 36, 37 and 146-150 are pending and currently under examination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-14, 16-20, 26-32, 36, 37 and 146-150 are provisionally rejected under the judicially created doctrine of double patenting over claims 26-88 of copending Application No. 09/968,958.

Applicant has indicated that consideration of filing a terminal disclaimer would be made once allowable subject matter was indicated. See appeal brief, page 5. Applicant's request is noted, however the rejection can not be held in abeyance. Therefore, the rejection is maintained for the reasons of record.

As noted in the previous office action, this is a provisional double patenting rejection since the conflicting claims have not yet been patented. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). In the instant case, the method set forth in claim 1 of the instant application is essentially the same as that set forth in claim 58 of '958. Further, it is noted that claim 26 of application '958

encompasses essentially the same invention as encompassed by claims 1 and 12 of '033. Dependent claims in each application set forth specific types and amounts of vectors, specific types of cancers, and specific times of administration that set forth inventions which are essentially the same in breadth between both applications.

Applicant is advised that should claim 1 be found allowable, claim146 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In the instant case, simply indicating the mechanism on how the method works does not distinguish the claimed method from that set forth in claim 1.

Response to Amendment

Applicant notes that the declaration filed June 13, 2002 (attached to comments regarding the decision from the BPAI), and the statement of Dr. Clayman supports that the invention was conceived and due diligence followed that antedates the November 1995 date of the cited references. See applicant's appeal brief, page 8. Applicant's arguments have been considered, and found persuasive.

The details of the information regarding applications for FDA trials and Grand Rounds seminar are sufficient evidence that the claimed invention was conceived prior to the publication of both Katayose and Srivastava references.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9, 13, 14, 16-20 and 36 rejected under 35 U.S.C. 102(b) as being anticipated by Liu *et al.* (IDS Reference) is withdrawn.

Applicant notes that Liu *et al.* teaches the method in an animal model, not for the treatment of humans as instantly claimed.

Examiner agrees with Applicants summary of the teaching of Liu *et al.*

Claims 1-9, 13, 14, 16-20 and 36 rejected under 35 U.S.C. 102(a) as being anticipated by Clayman *et al.* is withdrawn.

Review of the declaration provided in Exhibit J demonstrates that the Clayman *et al.* reference is not by another, therefore does not qualify as a 102(a) type reference.

Claims 1-14, 16-20, 26-32, 36 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Roth *et al.* (5,747,469 or 6,017,524) is withdrawn.

Examiner agrees with Applicants summary of the teaching of Roth *et al.*

Claims 1-14, 16-20, 26-32, 36, 37 146, 148 and 150 rejected under 35 U.S.C. 102(b) as being anticipated by Roth *et al.* (6,069,134) is withdrawn.

Claims 1-14, 16-20, 26-32, 36 and 37 rejected under 35 U.S.C. 102(b) as being anticipated by Vogelstein *et al.* (6,677,312) is withdrawn.

Applicants argue that neither Roth *et al.* (6,069,134) nor Vogelstein *et al.* (6,677,312) specifically teach to practice the method as claimed. More specifically, it is noted that all the working examples and general guidance in the art at the time of filing focused on replacing a mutant form of p53, not on expressing p53 in cells that express a normal p53 as recited and encompassed by the instant claims (see for example the preamble of claim 1). Applicants' arguments have been fully considered and found persuasive. Examiner agrees that while both references teach to provide p53 to kills cells in the treatment of cancer, neither specifically teach to use the strategy on a cell that expresses p53.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

> to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14, 16-20, 26-32, 36 and 37 rejected under 35 U.S.C. 103(a) as being unpatentable over Clayman *et al.* and Liu *et al.* in view of Zhang *et al.* is withdrawn.

Since the teaching of Clayman *et al.* 1 is not by another, the combined teaching fail to teach all of the limitations set forth in the claims.

Claims 1-14, 16-20, 26-32, 36, 37 and 146-150 are rejected under 35 U.S.C. 103(a) as being unpatentable over Srivastava *et al.*, Cajot *et al.*, Katayose *et al.*, Will *et al.*, Liu *et al.* and Zhang *et al.* is withdrawn.

As noted above, the declaration of Dr. Clayman was sufficient to obviate the use of either Srivastava *et al.* or Katayose *et al.* in the rejection. Without the teachings of these two references the rejection fails to meet the requirements of making a rejection under 35 USC 103.

Claims 1-14, 16-20, 26-32, 36, 37, 146-150 are rejected under 35 U.S.C. 103 as being unpatentable over Roth *et al.* (6,069,134), Liu *et al.*, Vogelstein *et al.* (6,677,312) in view of Baker *et al.* (Science 249(4971):912-915, Aug 24, 1990) and Shaw *et al.* (PNAS 89:4495-4499, May 1992).

The essential issue regarding Applicants arguments is that the cited art fails to teach the administration of a functional p53 to cells that already express p53. It is argued that the art focused on treating cancer by providing a functional copy of p53 to cells that did not express p53 or expressed mutant forms of p53. It has been argued that there is no motivation nor expectation

of success that administering p53 to cells that already have and express a functional p53 would have any affect in treating cancer, more specifically in the inhibition of tumor growth. At the time of filing Baker *et al.* teach the delivery and affect of wild-type p53 to cells that express an endogenous p53. All cell lines used by Baker *et al.*, the SW480, SW837, RKO and VACO235 cell lines, had endogenous expression of p53 (see for example Figure 1 or top of third column of page 913). Additional experiments demonstrated that wild type p53 dramatically inhibited growth of the cells and decreased DNA synthesis (page 914, first column). While the efficiencies differed among the cell lines tested, based on the evidence Baker *et al.* concluded that wild type p53 had a suppressive effect on growth (page 914, third column). The work of Shaw *et al.* demonstrates that the over-expression of wild type p53 causes cell cycle arrest at the G1-S boundry (page 4495, first column), and may result in apoptosis of the cell when observed *in vitro* or tumor regression *in vivo* (page 4497, second column). Thus, at the time of filing the inhibitory affect of p53 on the cell cycle and its ability to induce apoptosis in a tumor cell lines, even in cells that had expression of endogenous p53, was well documented. Moreover, the affect was seen and demonstrated both *in vitro* and in *in vivo* models. While it was clear that many forms of cancer in humans lose their functional p53 either through mutation or gene silencing through recombination of p53, and one focus of research aimed at restoring p53 activity in these cells, at the time of filing it is clear that over-expression of p53 results in the ability to inhibit the cell cycle and can result in apoptosis of the cell.

As noted previously, Roth *et al.* teach a method of treating a tumor by killing the cells of the tumor through the expression of p53 (see claim 1). The vector can be deliver by a variety of vectors including adenoviral vectors, and in conjunction with known chemotherapeutic agents

and protocols normally used alone in the treatment of tumors. Roth *et al.* teach to optimize deliver of specific a specific vector for different PFU and volumes and in part for the use of different types of promoters such as the CMV promoter. In the course of successfully practicing the claimed methods, Roth *et al.* teach that for effective treatment multiple times and multiple sites of delivery may be necessary to affect the entire tumor or the entire bed from which the tumor has been removed. While treatment was not affected in a human, the the model system was established to test for treating tumors in humans, and the specific cells used were in fact human cells. There would have been an expectation of success because the cells used in the model system were human, establishing that the methodology works in human tumor cells. Similarly, Liu *et al.* teach a method of reducing tumor burden in a mouse following the administration of an adenoviral vector encoding a wild-type p53 polypeptide. Liu *et al.* reduce to practice specifically administration to a squamous cell carcinoma in the model system used, however teach that the methods could be applied to other types of cancers. It is noted that Liu *et al.* does not reduce to practice the methods in humans, however animal models are used in the art as a means to make assessment of therapies for use in humans. The cells used in the model system are human to establish the affect in specific types of cancer and cancer cell types derived from human subjects. The adenoviral vector used in the methods is deleted of the E1 region and has a CMV promoter for expression of the p53 inserted therein. The vector is delivered surgically to a revealed tumor in 100ul volumes in increasing log increments up to 10^{12} PFU to test efficacy. It is noted that Liu *et al.* disclose the administration to lines Tu 138 and Tu 177, however they teach that other cell have been used (page 3663, bottom of first column) and teach the administration to K563 cells, a lymphoblastoma cell (page 3663, second column). Again,

while treatment was not specifically affected in a human the system was established such a treatment and the specific examples tested the effectiveness in human tumor cells. Vogelstein *et al.* teach a method wherein p53 is provided for the treatment of cancer. Vogelstein *et al.* teach that adenoviral vectors can be used, and the delivery can be tailored to the type of cancer be treated. Clearly, the results of Baker *et al.* and Shaw *et al.* the affect of p53 can be affected in cancer that maintains endogenous expression of p53, provides evidence that the methods set forth by Roth *et al.* Liu *et al.*, and Vogelstein *et al.* can be applied to any cell type in any cancer, not exclusively to cells that have a mutated p53. p53 has a role in both cell cycle and the transformation process, and though it can be an important marker in human cancers, the results of Baker *et al.* and Shaw *et al.* demonstrate that the cell cycle inhibitory affect of p53 can be accomplished by over-expression even in the presence of endogenous p53. This observation is important because it was recognized that the etiology of cancer can vary from cancer type, and even cell to cell within a tumor. One would have been motivated to treat all forms of cancer, p53 positive and p53 negative, with the methods of Roth *et al.* Liu *et al.*, and Vogelstein *et al.* in light of the results of Baker *et al.* and Shaw *et al.* who clearly demonstrate that the cell cycle inhibitory affect of p53 can be accomplished by over-expression even in the presence of endogenous p53. Moreover, in addition to cell cycle arrest, the over-expression of p53 can induce apoptosis which results in the inhibiting and regression of tumor growth There would have been a reasonable expectation of success to practice the methods of Roth *et al.* Liu *et al.*, and Vogelstein *et al.* with any tumor type, i.e. p53 positive or p53 negative, given the results of both Baker *et al.* and Shaw *et al.*

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

'"Phase III Gene therapy trial approved for head neck cancers" (Reuters Health, March 13, 2000), provides evidence for the use of p53 in phase I trails as early as 1995, and that active collaborations between Introgen and Hone-Poulenc were active as early as 1994.

"Therapeutics and Rhone-Poulenc Rore to collaborate on gene therapy programs for cancer", (Introgen Theraputics, Inc. -in the News October 27, 1994) provides the basis of using p53 in light of its activity with K-RAS and;

"Intorgen Therapeutics now has largest in vivo cancer portifolio in field of gene therapy" (Introgen Theraputics in the News November 8, 1995) provides evidence that Dr. Clayman and Dr. Roth had started pre-clinical trials for head and neck cancer, and non-small cell lung carcinoma (NSCLC) using the delivery of normal p53.

Eliyahu *et al.* PNAS 86:8763-8767 (November, 1989) investigates the paradox of p53 function in neoplastic development, and provides evidence for the inhibitory affect of p53 on the cell cycle and its role with other factors in the transformation process.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

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